REMARKS

In the Final Action dated June 26, 2008, claims 11, 13 and 15 are pending and are under consideration. Claims 11 and 15 are rejected under 35 U.S.C. §102(e) as being anticipated by Ghosh et al. (US 6,268,398) ("Ghosh") with evidence by Lang et al. (US 2005/0064501) ("Lang"). Claims 11, 13 and 15 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ghosh in view of Thiam et al., (FEBS Letter, 1999) ("Thiam") with evidence by Lang et al. (US 2005/0064501).

It is respectfully noted that although the Applicant does not agree with the rationale underlying the aforementioned rejections, in order to expedite the allowance of the claims, the Applicant has canceled claims 11, 13 and 15 without prejudice, and added new claims 16-21. Support for new claims 16-21 is found in the specification as follows: claims 16-17 (see specification, page 6, lines 20-25; page 15, lines 15-19; page 16, lines 28-29); claims 18-21 (see page 10, lines 21-27; page 20, lines 18-21; Fig. 5 and page 8, lines 2-4). It is believed that the amendments filed herewith do not introduce new matter into the application.

Comments Relating to the Cited References

New claims 16-21 are directed specifically to decreasing the synaptic transmission of a mammalian neuron, wherein the synaptic transmission comprises long-term potentiation. The Examiner's rejection of pending (but canceled herewith) claims 11, 13 and 15 is based on an inherency. It is longstanding practice that in order to establish a *prima facie* case of anticipation, it must be shown that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.1987). See MPEP § 2131. It is

further critical that "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (B.P.A.I. 1990) (Emphasis added). In the present case, Ghosh, as evidenced by Lang, does not provide or teach each claim limitation explicitly or inherently.

In fact, it is respectfully submitted that the teachings of Ghosh and Lang are, in fundamental ways, the opposite of what is alleged in the Office Action of June 26, 2008. Thus, Applicant provides below specific comments relating to the disclosures of Ghosh and Lang, and indicates why these references do not disclose the technical features as alleged in the Office Action.

Office Action's First Allegation – page 3; third paragraph

Ghosh et al. teach the method of administering chelerythrine as kinase inhibitors for therapy of diseases including Alzheimer's disease, diabetes mellitus, neuropathy, epilepsy, stroke and traumatic injury to the brain (columns 2, 4, 6, 17-20, and 22). (Emphasis added).

Response to Office Action's First Allegation

Ghosh teaches administering chelerythrine as an apoptosis-inducing compound. Apoptosis is a normal process in a cell that leads to its death. Some characteristics of apoptosis are membrane blebbing, fragmentation and disintegration, altered permeability, and the like (see Ghosh, col. 23, lines 1-20). In other words, Ghosh proposes to initiate cell death in order to study the effects of various mitochondrial protectants, which comprise the putative therapeutic agents. (Col. 22, line 5, *et seq.*). Ghosh does not disclose administering chelerythrine for any therapeutic process whatsoever. Nor does Ghosh explicitly or inherently disclose any effect on decreasing long term potentiation at a synapse. Clearly, the decrease in long term potentiation of

synaptic transmission disclosed and claimed in the instant application is not contemplated by killing the relevant neurons.

Ghosh does not show any effect resulting from administering chelerythrine. Put another way, Ghosh's mere reference to chelerythrine as an apoptogen does not satisfy the rule in *Ex Parte Levy* requiring that the alleged inherent characteristic necessarily flows from the teachings of Ghosh's disclosure. In fact Ghosh does not even contain the term "synaptic transmission" or "long term potentiation."

Therefore, it is respectfully submitted that Ghosh does not establish a *prima facie* case of inherent anticipation.

Office Action's Second Allegation – page 3; third paragraph

The Office Action alleges that: Lang et al. teach that the chelerythrine suppresses the activation of the Na+ channel (page 1, paragraph 0023, 0052-0057); Lang et al. teach treatment of epileptic seizure with kinase inhibitors (page 2, paragraph 0028); Lang et al. teach diagnosing of epilepsy, hypertension, fibrosing pancreatitis, radiation fibrosis, scleroderma, cystic fibrosis, chronic bronchitis using tissues of brain, Alzheimer's disease, cirrhosis of the liver, Crohn's disease, fibrosing pancreatitis and pulmonary fibrosis, arteriosclerosis, diabetic nephropathy.

Applicant's Response to Office Action's Second Allegation

The Office Action alleges that Lang et al. evidence the anticipatory nature of Ghosh because, *inter alia*, Lang et al. disclose that chelerythrine suppresses the activation of the Na+ channel, i.e., "ENaC" (page 1, paragraph 0023, 0052-0057). It is respectfully submitted that this teaching by Lang et al. is not relevant to the pending or newly added claims, and as discussed below, results in an incorrect interpretation of the art.

ENaC is an acronym for Epithelial Sodium Channel (see Lang [0005]). This ion channel is found in epithelial tissue and not neurons. Of far more relevance is the neuronal sodium channel, which constitutes a distinct family of sodium channels. The experiment in Lang et al. relied upon in the Office Action is shown in Fig. 4. Lang et al. demonstrates that coexpressing h-sgk kinase with the ENaC in oocytes activates ENac. Lang et al. further demonstrates that the activation is inhibited by chelerythrine. However, as stated above and discussed below, ENaC is not the neuronal sodium channel, and is not involved in neuronal excitability and synaptic transmission. The neuronal sodium channel is referred to as MDEG and is also explored in Lang et al. (see paragraph [0006]).

Lang et al's coexpressed neuron-specific MDEG with h-sgk in oocytes (see Lang, Fig. 6, and page 3, col. 1, [0057]). However, in contrast to the result with the epithelial channel ENaC, when MDEG is co-expressed with h-sgk, the channel is completely blocked (compare with Lang et al's demonstration that ENaC requires activation by h-sgk to assume a functional state). Lang et al. states "it must be concluded from this that h-sgk inhibits neuronal excitability." (Page 3, col. 1, [0057]). Therefore, any compound that inhibits h-sgk should enhance neuronal excitability. The clear implication for the instant Office Action is that administering the drug chelerythrine to a cell expressing the neuronal sodium channel (i.e., a neuron), would inhibit h-sgk (see Lang et al., Fig. 1), thereby promoting neuronal excitability. This is the exact opposite of the claimed subject matter in that chelerythrine is shown to inhibit synaptic transmission, i.e., long-term potentiation (see specification Fig. 2).

It is respectfully submitted that Lang et al. cannot reasonably be interpreted as evidencing the disclosure of Ghosh. There is virtually no connection between Ghosh's suggestion to experimentally induce cell death with chelerythrine as a screen to test

mitochondrial protectants, and Lang et al's explicit teaching that h-sgk kinase regulation of MDEG inhibits post-synaptic transmission. This latter effect is the exact opposite provided by PKMζ, which maintains LTP across neuronal synapses. Accordingly, the drug chelerythrine also has opposite effects.

Office Action's Third Allegation – page 5; fourth paragraph

One of ordinary skill in the art would have been motivated to modify the method of Ghosh et al. because Ghosh et al. explicitly consider chelerythrine, Staurosporine or other kinase inhibitors and the pseudosubstrate peptide of Thiam et al. is a kinase inhibitor. Furthermore, one of ordinary skill in the art would have been motivated because Thiam et al. is an analogous art with Lang et al. because both use kinase inhibitors.

Applicant's Response to Office Action's Third Allegation

It is respectfully submitted that Ghosh's mere reference to protein kinase inhibitors as a means to induce apoptosis (col. 22, lines 33-38) would not remotely induce persons of ordinary skill in the art to expect that they would be able to impair long term potentiation in neurons by adding any of the listed inhibitors. The terms "long term potentiation," "voltage," and "synapse," and other related terms do not even appear in Ghosh. Further, Thiam's pseudosubstrate inhibitors are used to induce apoptosis in a T lymphocyte cell line and a promyelocytic leukemia cell line. Thiam does not describe any aspects of neuronal synaptic transmission or its regulation by protein kinases. In general, these two references describe ways to induce cell death via protein kinases, and other means.

The only cited reference that even remotely deals with the subject application is Lang et al's experiments with kinase regulation of a neuronal ion channel. However, as stated

above, Lang et al. disclose the exact opposite conclusion on how the respective kinases regulate synaptic activity.

In sum, it is respectfully submitted that Ghosh, taken individually or as evidenced by Lang et al. or Thiam et al., does not explicitly or inherently anticipate the pending claims (now canceled herewith) and the newly submitted claims.

Response to Office Action

Claims 11 and 15 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Ghosh with evidence by Lang et al. Ghosh allegedly teaches the method of administering chelerythrine as kinase inhibitors for therapy of many diseases including Alzheimer's disease, diabetes mellitus, neuropathy, epilepsy, stroke and traumatic injury to the brain (columns 2, 4, 6, 17-20, and 22).

Although Applicant disagrees with the rejection, Applicant has canceled claims 11 and 15, without prejudice and new claims 16-21 have been added. The new claims are directed to a method of decreasing neuronal synaptic transmission wherein the synaptic transmission comprises LTP.

It is respectfully submitted that Ghosh, with evidence of Lang et al., does not explicitly or inherently teach methods of down-regulating neuronal synaptic transmission in general, let alone LTP specifically. Accordingly, it is believed that the amendment overcomes the rejection and that the claims are in condition for allowance.

Claims 11, 13 and 15 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ghosh in view of Thiam et al., (FEBS Letter, 1999) ("Thiam") with evidence by Lang et al. (US 2005/0064501). The Examiner alleges that one of ordinary skill in the art would have been motivated to modify the method of Ghosh et al. because Ghosh et al. explicitly

consider chelerythrine, Staurosporine or other kinase inhibitors and a pseudosubstrate peptide of Thiam et al. is a kinase inhibitor. The Examiner further alleges that one of ordinary skill in the art would have been motivated because Thiam et al. is an analogous art with Lang et al. because both use kinase inhibitors.

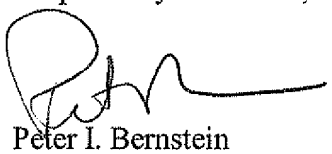
Applicant respectfully disagrees but to expedite prosecution, has canceled claims 11 and 15 without prejudice and added new claims 16-21. The new claims are directed to a method of decreasing neuronal synaptic transmission wherein the synaptic transmission comprises LTP.

It is respectfully submitted that Ghosh, with evidence of Lang et al., in view of Thiam, does not explicitly or inherently teach methods of down-regulating neuronal synaptic transmission in general, let alone LTP specifically. The limitations of Ghosh and Thiam have been discussed above in detail, as was the clearly contrary teachings of Lang et al. This combination of references does not teach or suggest claim limitations pertinent to a method of decreasing neuronal synaptic transmission wherein the synaptic transmission comprises LTP. Further, Lang et al. show that inhibiting the h-sgk kinase would stimulate synaptic transmission, and therefore, teaches away from the proposition governing the Examiner's citation of the art, as well as the claimed subject matter.

Accordingly, it is believed that the present amendment overcomes the rejection and that the claims are in condition for allowance.

This Response addresses each of the Examiner's rejections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all newly added claims is therefore respectfully requested.

Respectfully submitted,



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